UNITED STATES PATENT AND TRADEMARK OFFICE

**BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES**

Ex parte ADRIANO AGUZZI,
MICHAEL A. KLEIN, ALEX RAEBER,
CHARLES WEISSMAN, and ROLF ZINKERNAGEL

Appeal 2007-2226
Application 09/554,567
Technology Center 1600

Decided: August 14, 2007

Before TONI R. SCHEINER, ERIC GRIMES, and NANCY J. LINCK, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of identifying B-cells infected with prions. The Examiner has rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

BACKGROUND

"Transmissible spongiform encephalopathies (TSE's) comprise a group of slow degenerative diseases of the CNS [central nervous system]

such as Creutzfeldt-Jakob disease (CJD), new variant CJD (termed nvCJD), Gerstmann-Sträussler-Scheinker disease (GSS) and kuru in man and scrapie in sheep or BSE (mad cow disease) in cattle" (Specification 1, citations omitted). The causative agent of these diseases appears to be a protein called a "prion" (*id.* at 2). "Considerable evidence now supports the 'protein only' hypothesis which proposes that the prion is devoid of nucleic acid and identical with PrP^{Sc}, a modified form of PrP^{C}. PrP^{C} is a normal host protein. . . . PrP^{Sc} is defined as a protease-resistant form of PrP^{C}. . ." (*id.* at 2-3, citations omitted).

The Specification discloses "an assay method for determination of the presence of [TSE]-infected B-cells in humans or animals or in body fluid or tissue derived products isolated therefrom" (*id.* at 9). Preferred assay methods include "Western blots carried out with presumably [TSE]-infected B-cells" (*id.* at 9-10). Thus, B-cell fractions can be electrophoresed through SDS polyacrylamide gels after treatment with proteinase K, blotted onto nitrocellulose, and PrP visualized with an anti-PrP monoclonal antibody (*id.* at 112).

DISCUSSION

1. CLAIMS

Claims 35-37 are pending and on appeal. Appellants argue the claims "together as a group" (Br. 6).[1] The claims therefore stand or fall together. 37 C.F.R. § 41.37(c)(1)(vii).

Claim 35 is representative and reads as follows:

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[1] Appeal Brief filed October 10, 2006.

35. A method of identifying TSE-infected B-cells associated with transmissible spongiform encephalopathy in a test sample, the method comprising the steps of:

obtaining a test sample suspected of TSE infection;

collecting B-cells from the test sample;

subjecting said B-cells to homogenization;

subjecting said homogenized B-cells to proteinase K digestion;

subjecting said digested B-cells to SDS Page immunoaffinity chromatography blots;

contacting said blots with an anti-PrP antibody,

wherein the presence of a signal from said anti-PrP antibody-PrP complex in the sample is indicative of TSE-infected B-cells;

identifying TSE-infected B-cells based on the presence of said signal; and

wherein the identification of TSE-infected B-cells is associated with TSE promulgation and primary infection.

Thus, claim 35 is directed to a process of identifying B-cells infected with TSE. B-cells from a test sample suspected of being infected are homogenized, and then digested with proteinase K. The digested B-cells are then subjected to SDS-PAGE and blotting. The blot is contacted with an anti-PrP antibody. Binding of the anti-PrP antibody to PrP on the blot indicates that the cells from the sample were infected with TSE.

2. PRIOR ART

The Examiner relies on the following references:

O'Rourke US 6,165,784 Dec. 26, 2000

C. Korth et al., *Prion (PrP^{Sc})-specific epitope defined by a monoclonal antibody*, 390 Nature 74-77 (November 6, 1997).

Yasuo Kuroda et al., *Creutzfeldt-Jakob Disease in Mice: Persistent Viremia and Preferential Replication of Virus in Low-Density Lymphocytes*, 41(1) Infection and Immunity 154-161 (July 1983).

Elias E. Manuelidis et al., *Viremia in Experimental Creutzfeldt-Jakob Disease*, 200 Science 1069-1071 (June 2, 1978).

3. OBVIOUSNESS

Claims 35-37 stand rejected under 35 U.S.C. § 103 as obvious over "O'Rourke et al and/or Korth et al in view of Kuroda et al. and/or Manuelidis et al." (Answer 3).

The Examiner cites O'Rourke as disclosing an assay for TSE in lymphoid tissue comprising the steps of "tissue homogenization, treatment with proteinase K, separation on polyac[r]ylamide gel, transfer to a filter and contacting the filter with a monoclonal antibody to detect the presence of prion in the tissue sample" (*id.* at 4). The Examiner cites Korth as using a monoclonal antibody capable of distinguishing between the prion and cellular forms of PrP in an assay having the steps of homogenizing brain tissue, immunoprecipitating with a monoclonal antibody, digesting the sample with proteinase K, Western Blotting, and detecting the prion on the Western-blot using an anti-PrP antibody (*id.* at 5).

The Examiner concedes that "[n]either O'Rourke et al nor Korth et al teach the detection of TSE in B cell[s]" (*id.*). To meet this limitation, the Examiner cites Kuroda as disclosing that "B cells . . . can transmit TSE," and Manuelidis as disclosing that "it is important to focus on these cellular populations (buffy coat) to increase the sensitivity of assays for TSE infectivity" (*id.*).

The Examiner concludes that one of ordinary skill would have considered it obvious "to improve the sensitivity of the TSE tests by collecting samples containing B cells . . . and testing for the presence of TSE using an antibody-based system" (*id.* at 5-6). The Examiner reasons that "[t]he ordinary artisan at the time the invention was made would have reasonably expected that concentrating a cell type known to be infected with the TSE agent would increase the sensitivity of detection assays, including antibody-based assays" (*id.*).

"The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art." *In re Young*, 927 F.2d 588, 591, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). We agree with the Examiner that the cited references would have made the process recited in claim 35 obvious to one of ordinary skill. Specifically, it would have been obvious to use prion-specific antibodies to assay B-cells for TSE according to the methods of O'Rourke or Korth, because Kuroda teaches that B-cells transmit CJD, a type of TSE, and therefore necessarily contain the TSE-causing agent.

Appellants argue that "[t]he Examiner's rejection is erroneous . . . [because] neither Kuroda nor Manuelidis explicitly teach that B-cells and/or T-cells can transmit TSE" (Br. 7). Appellants note that the authors of both references incorrectly thought that the disease-causing agent of TSE was a virus, rather than an abnormal prion (*id.* at 8). Appellants argue that because Kuroda and Manuelidis were incorrect regarding the "nature of the disease-causing agent and were not even aware of the existence of prions, the references simply cannot render obvious the method involving the steps of

collecting B-cells and/or T-cells from a test sample and directly testing these cell types for the presence of prions associated with TSE" (*id.* at 9). Appellants argue that "it is more likely that a skilled artisan would either agree with Kuroda and Manuelidis that CJD is a viral infection (and in that case, would not be motivated to test for abnormal prions) or disregard the references completely (and in that case, would not be motivated to concentrate lymphocyte cells)" (*id.* at 10).

We do not find this argument persuasive. Regarding CJD, Kuroda discloses that "[i]nfectivity was found in both T-cell and B-cell fractions, but much higher infectivity was found in the B-cell fraction" (Kuroda 158, left column). Kuroda also discloses that 16 of 18 mice died after receiving B-cell fractions from infected mice (*id.* at 159, Table 4). Kuroda's explicit disclosure that B-cells transmit TSE would have suggested to one of ordinary skill that B-cells necessarily contain the disease's causative agent.

We do not agree that Kuroda's teachings are undermined by its incorrect assumption that the disease was caused by a virus. "In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581, 35 USPQ2d 1116, 1123 (1995) (internal quotations omitted). Thus, "[n]on-obviousness cannot be established by attacking references individually where the rejection is based upon the teachings of a combination of references. . . . [The reference] must be read, not in isolation, but for what it fairly teaches in combination with the prior art as a

whole." *In re Merck & Co.*, 800 F.2d 1091, 1097, 231 USPQ 375, 380 (Fed. Cir. 1986).

Section 103(a) requires an assessment of whether the prior art renders the claims obvious "at the time the invention was made," not at the time the earliest prior art was published. At the time of Appellants' invention it was known that prions, the causative agent of TSE, could be detected by probing an SDS-PAGE protein blot, i.e. Western blot, of diseased tissue with prion-specific antibodies (*see* O'Rourke, col. 6, ll. 45-55; *see also* Korth 75, Figure 1). It was also known that B-cells contain the agent that causes TSE (*see* Kuroda 158-159). We agree with the Examiner that one of ordinary skill, viewing these teachings in combination, would have reasoned that probing an SDS-PAGE protein blot of B-cells with a prion-specific antibody would detect the presence of prions if the animal were infected with TSE.

Appellants argue that because Kuroda and Manuelidis incorrectly identified the TSE-causing agent as a virus rather than a prion, one of ordinary skill would not have been motivated to combine those disclosures with O'Rourke and Korth, which identify prions as the causative agent (Br. 11-14). Appellants argue that because "the emerging scientific consensus was that the infective agent of TSE was not a virus," one of ordinary skill would have heavily discounted the disclosures of Kuroda and Manuelidis, and not combined them with O'Rourke and Korth (*id.* at 14). Appellants urge that one of ordinary skill would only have arrived at the claimed invention through hindsight gleaned from the instant Specification (*id.* at 15).

We are not persuaded by this argument. Recently addressing the issue of obviousness, the Supreme Court stated that the analysis under 35 U.S.C. § 103 "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 USPQ2d 1385, 1396 (2007). The Court advised that "[a] person of ordinary skill is . . . a person of ordinary creativity, not an automaton." *Id.* at 1742, 82 USPQ2d at 1397. Regarding hindsight reasoning, the Court noted that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *Id.* (citations omitted).

In the instant case, the data in Kuroda demonstrate that the TSE-causing agent was present in B-cells from infected animals (*see* Kuroda 158-159). Armed with the knowledge imparted by O'Rourke and Korth that prions, not viruses, were the cause of TSEs, one of ordinary skill, being a person of ordinary creativity and common sense, would not have discounted this aspect of Kuroda's disclosure, because the data demonstrating infectivity in B-cells do not relate to whether the infectious agent is a virus or protein. Rather, one of ordinary skill at the time of Appellants' invention would have inferred that the infectious agent, whatever it was, would be present in B-cells and detectable therein by available prior art methods. We therefore agree with the Examiner that, in view of Kuroda, one of ordinary skill practicing the antibody-based TSE detection techniques of O'Rourke

and Korth would have considered it obvious to apply those techniques to B-cells, as recited in claim 35.

Appellants argue that Korth teaches away from the method recited in claim 35 because Korth discloses that "the identification of an antibody that binds selectively to PrP^{Sc} from various species provides a new means to identify PrP^{Sc} directly *without using proteinase K digestion as a criterion*" (Br. 16, quoting Korth 77 (emphasis Appellants')). Thus, Appellants argue, Korth suggests avoiding the step of proteinase K digestion that is explicitly recited in claim 35 (*id.* at 16-17).

The Examiner responds that, while proteinase K does not digest PrP^{Sc}, it digests other cellular proteins including normal prion proteins, thereby improving PrP^{Sc} isolation from other cellular proteins. (Answer 10). The Examiner reasons that "one would have been motivated to treat the homogenized sample with proteinase K because an increased isolation of abnormal prion protein would lead to a greater signal to noise ratio following contacting the blots with an anti-PrP antibody" (*id.* at 10-11).

We do not agree that Korth teaches away from practicing the method recited in claim 35. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Kahn*, 441 F. 3d 977, 990, 78 USPQ2d 1329, 1338 (Fed. Cir. 2006) (quoting *In re Gurley*, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994)).

While Korth discloses that the 15B3 antibody is able to identify PrP^{Sc} without proteinase K digestion, Korth does not state that proteinase K

digestion should be omitted when using the antibody to detect PrP^{Sc} on a Western blot. Indeed, Korth discloses using the 15B3 antibody to detect PrP^{Sc} in Western blots of proteinase K-digested tissue homogenates (Korth 75, e.g. Figure 1b).

Moreover, claim 35 encompasses using antibodies other than Korth's 15B3, such as the antibodies disclosed in O'Rourke. O'Rourke explicitly discloses that homogenized tissue subjected to Western blot analysis for TSE detection should be "treated with proteinase K to eliminate the 35 K PrP-C band and reveal the characteristic multiple 28-32 K bands of proteinase K-resistant PrP-Sc fragments" (O'Rourke col. 6, ll. 46-48). Thus, consistent with the Examiner's analysis, O'Rourke discloses that proteinase K digestion improves detection of PrP^{Sc}. We therefore agree with the Examiner that Korth does not teach away from performing the proteinase K digestion step recited in claim 35.

SUMMARY

We agree with the Examiner that one of ordinary skill practicing the TSE detection techniques of O'Rourke and Korth would have considered it obvious to apply those techniques to B-cells, in view of Kuroda's disclosure that B-cells contain the TSE-causing agent. We therefore affirm the Examiner's obviousness rejection of claim 35. Because claims 36 and 37 were not argued separately, they fall with claim 35. 37 C.F.R. § 41.37(c)(1)(vii).

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

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